EFFECT OF ALTERED BLOOD FLOW ON THE CALIBER AND MORPHOLOGY OF THE INTERNAL THORACIC ARTERY IN THE DOG

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***Objective:* The purpose of this study was to evaluate in dogs the effect of blood flow alteration on caliber and morphology of in situ internal thoracic arteries. *Methods:* Six dogs underwent creation of a unilateral distal arteriovenous fistula between the internal thoracic artery and vein at the sixth rib to create high flow, and in six others the internal thoracic artery was unilaterally skeletonized and dissected. For both groups the contralateral internal thoracic artery served as the control; sides were alternated among cases. Blood flow was measured for shear stress calculation before and after surgical alteration. After 2 months, internal thoracic arteries were harvested with the entire anterior chest plate, which was dynamically inflated and fixed with 10% formalin at a controlled pressure of 120 mm Hg after angiography had been done at the same pressure. The luminal diameters were then measured at eight levels on the angiograms. Arterial tissue samples were taken at three levels and embedded, sectioned, and treated with hematoxylin-eosin and Verhoeff-van Gieson stains. Digital imaging analysis was used for quantitative morphometric studies. *Results:* All fistulas remained patent. In comparison with control arteries, high-flow internal thoracic arteries dilated and low-flow internal thoracic arteries narrowed, which was associated with significant change in shear stress for both groups. There were no substantial structural changes in the walls of either group. *Conclusion:* In the dog, the luminal diameter of the internal thoracic artery responds to altered blood flow without intimal thickening or other undesirable wall changes. (J Thorac Cardiovasc Surg 1997;113:114-20)**

Use of the internal thoracic artery (ITA) as a coronary artery bypass graft is becoming more common because of its superior long-term patency.[1-5] However, a diffuse narrowing of the distal portion of a few ITA grafts, described as a "string sign" or "distal thread phenomenon," has been noted.[6-10] The cause of this phenomenon has been attributed to a low-flow rheologic state in the ITA graft that results from anastomosing it to a coronary artery with only a minor degree of proximal stenosis. Barner[6] introduced the concept of "disuse atrophy" as a mechanism for this narrowing. The disappearance of a low-flow-initiated "string sign" was observed when high flow through the ITA was restored.[8, 10] This reversible phenomenon may suggest that decreasing flow could cause the ITA to contract in a rheologically directed effort toward maintenance of a suitable shear stress on the arterial wall. It has also been reported that high flow through the ITA causes its caliber to increase.[11, 12] Although these clinical findings suggest that changes in the caliber of the ITA correlate with graft flow, there have been no experimental studies to characterize this correlation. The purpose of this study was to evaluate the effect of altering the blood flow on the caliber and morphology of the in situ ITA in dogs during a 2-month period of observation.

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Material and methods

Twelve healthy mongrel dogs, weighing 21.0 to 29.0 kg (average weight 24.3 kg, SD* 0.6 kg), were used in this study. All animals were cared for in compliance with the

*Standard deviation.

"Guide for the Care and Use of Laboratory Animals" prepared by the National Institutes of Health (NIH Publication No. 80-23, revised 1985).

The animals were divided into two groups: a high-flow (HF) group, in which a unilateral distal arteriovenous fistula (AVF) was created between the ITA and vein at the sixth rib site, and a low-flow (LF) group, in which the ITA was unilaterally skeletonized and dissected with bipolar cauterization, as previously described.[13] Both groups were studied in a paired comparison form, in which one ITA was altered as described and the contralateral ITA was left untouched to serve as the control; sides were alternated among cases.

Surgical procedures. After premedication of the dogs with acepromazine, 0.25 mg/kg, and atropine, 0.01 mg/kg, anesthesia was induced with 5 to 10 ml of 4% thiamylal intravenously and the animals were intubated. The anesthesia was then maintained with a combination of 0.5% to 1% halothane and a mixture of nitrous oxide and oxygen in a 2:1 ratio via an endotracheal tube connected with a closed-circuit respirator.

HF group (n = *6).* With the dog in the supine position, the operative field was disinfected and draped. A parasternal incision approximately 7 cm long was made, and the ITA and vein were approached after removal of a short segment of the sixth rib cartilage. A side-to-side AVF, approximately 5 mm long, was created between the ITA and vein at the sixth rib level with the use of running 8-0 Prolene polypropylene sutures (Ethicon, Inc., Somerville, N.J.).

LF group (n = *6).* The dog was placed in the lateral decubitus position. Under one skin incision two thoracotomies were made through the fourth and seventh intercostal spaces. The entire length of the ITA was skeletonized and dissected down to its bifurcation into the superior epigastric and musculophrenic branches with bipolar cauterization (Davol Electro Medical System, Englewood, Colo.). During the dissection, the branches were carefully cauterized three times, one second per time, by gently squeezing the bipolar cautery forceps along a 2 mm wide zone beginning 2 mm distal to the origin of the branches. The branch was then cut with scissors in the middle of the cauterized zone.[13]

ITA blood flow in both groups was measured both before and after the surgical alteration with a Transonic flowmeter, which directly measures the flow rate, rather than the flow velocity (model T-208, Transonic Systems, Inc., Ithaca, N.Y.), with a 3 mm probe on the ITA. Blood flow was measured just proximal to the AVF at the sixth rib level of the ITA in the HF group and at the proximal portion of the ITA in the LF group. Wounds were closed when the fields were completely dry. Appropriate antibiotics were given on the day of operation and for the next 10 days thereafter.

Specimen retrieval and angiographic evaluation. All specimens were retrieved 8 weeks after operation. The animals were pretreated with acepromazine and deeply anesthetized with thiamylal sodium. Both ITAs were accessed proximally via the supraclavicular approach. Blood flow rates were then simultaneously measured with a two-channel Transonic model T-208 flowmeter with 3 mm probes at the same level of the proximal ends of both ITAs. After administration of a 3 mg/kg dose of heparin the entire anterior chest plate, about 30 cm long × 25 cm wide and including both ITAs, was harvested as an intact single specimen. In the HF group, the internal thoracic vein was ligated 15 mm away from the AVFs, both proximally and distally.

Bilateral ITA angiography with a posteroanterior projection of the harvested chest plate was then done. ITAs were opacified by injection of 15 ml of Conray 60% iothalamate meglumine solution (Mallinckrodt Medical, Inc., St. Louis, Mo.) with 120 mm Hg pressure through two small, connected angiocatheters, which were placed in the proximal ITAs. The luminal diameters at eight levels of the ITAs, from the first to eighth rib sites, were measured with a digital caliper (model CD-6BS, Mitutoyo Corp., Utsunomiya, Japan). Each diameter reported in the results section was the actual luminal diameter after correction of magnification with the original length scale projected on the angiogram.

Morphologic evaluation of the arterial wall. The ITAs, with the whole chest plate, were dynamically inflated and fixed via the two angiocatheters used for angiography: 10% formalin was maintained at 120 mm Hg with a perfusion system for 24 hours, and the specimen was kept in formalin for an additional 2 days. Cross-section tissue samples from both the control and study ITAs were taken for light microscopy from the proximal (at the second rib), middle (at the fifth rib), and distal (at the eighth rib) sites. The tissue samples were embedded, sectioned, and treated with hematoxylin-eosin and Verhoeff-van Gieson stains. Digital imaging was used for quantitative morphometric studies. The image was transferred from histologic slides to microscopic photoprints, from which the image was scanned with a Relisys image scanner (Avec model 2400, Milpitas, Calif.). The magnification factor was eliminated by a standard micrometer scale during this processing. The cross-sectional areas (in square millimeters) of the arterial lumen, the intima, the media, and the adventitia were measured and the luminal radius, intimal thickness, medial thickness, and whole wall thickness (in millimeters) were calculated with an image analysis system (Macintosh computer with National Institutes of Health image 1.55). The morphometric data were used for subsequent data analysis.

Shear stress. To further analyze the relationship between the rheologic measurements and morphologic observations, shear stress was calculated. Shear stress was considered to be the force causing the morphologic change. Mean shear stress was calculated from the flow rate measured during specimen retrieval, and the luminal diameter at the site corresponding to the flow measurement was measured from the angiogram by the Hagen-Poiseuille formula

$$\tau = \frac{4\mu Q}{\pi r^3}$$

where τ is shear stress (in dynes per square centimeter), μ is viscosity (assumed to be 035 poise), Q is blood flow rate (in milliliters per second), and r is luminal radius (in centimeters).

Table I. *Hemodynamic alterations and measurement*

	Control	*Study ITA*	*p Value*
HF group			
Blood flow at beginning of study (before/after alteration) (ml/min)*		19.7 ± 9.9/183 ± 101	0.003
Blood flow at end of study (ml/min)†	62.8 ± 42.0	306 ± 251	0.040
Mean shear stress (dynes/cm^2)	19.6 ± 15.4	58.8 ± 39.8	0.035
LF group			
Blood flow at beginning of study (before/after alteration) (ml/min)‡		51.7 ± 32.1/13.3 ± 10.3	0.0003
Blood flow (ml/min) at end of study†	35.3 ± 5.4	10.7 ± 2.3	0.0001
Mean shear stress (dynes/cm^2)	10.3 ± 1.79	3.73 ± 1.04	0.0001

Values given as mean plus or minus the standard deviation. p Values indicate significant differences in all the comparisons.
*Measured at sixth rib level.
†Measured at the proximal end.
‡Measured in the proximal area.

Statistical analysis. The quantitative morphometric data were expressed as the arithmetic mean plus or minus the standard deviation. Statistical analysis was done with the Student's t test for paired samples obtained from the control and study specimens. Statistical significance was defined as $p < 0.05$.

Results

Measurement of blood flow rate. All AVFs remained patent. During operation the blood flow rate increased an average of 9.9 times (95% confidence interval [CI], 6.7 to 13.1) through the ITA (measured at the sixth rib level) after the creation of the AVF (from an average of 19.7 ml/min [SD 9.9] to 183 ml/min [SD 101], $p = 0.03$). During specimen retrieval, the HF group showed an average flow rate in the operated ITA 6.2 times higher than that in the contralateral control ITAs (95% CI, 2.4 to 10.0), measured at the proximal site of the ITA (306 ml/min [SD 251] versus 62.8 ml/min [SD 42.0], $p = 0.04$) (Table I).

During operation, the skeletonized, dissected ITAs exhibited an average 73.5% flow reduction (95% CI, 66.7 to 79.9), measured at the proximal portion of the ITA (from 51.7 ml/min [SD 32.1] to 13.3 ml/min [SD 10.3], $p = 0.0003$). At the end of the study, the LF group had an average flow rate 69.0% less than that in the contralateral control ITAs (95% CI, 61.0 to 77.0), measured at the proximal end of the ITA (10.7 ml/min [SD 2.3] versus 35.3 ml/min [SD 5.4], $p = 0.0001$) (Table I).

Angiographic findings. Angiograms revealed a dilation of the HF group ITAs with the AVF in comparison with the control ITAs (Fig. 1, *A*). The average luminal diameter measurements given in Fig. 1, *B,* demonstrate a statistically significant difference along the length proximal to the AVF, but not beyond the AVF. On the other hand, angiograms revealed a shrinkage (or narrowing) of the LF group ITAs with skeletonized dissection in comparison with the control ITAs (Fig. 1, *C*) and a significant difference in the average measured diameter along the entire length, except at the first rib level (Fig. 1, *D*).

Histologic morphologic studies. Histologically, except for the morphologic dimension, there was no substantial structural change in the wall, including no intimal thickening, in either the HF or LF groups after flow alteration.

For the HF group ITAs, the luminal area was significantly increased by an average of 14.0% (95% CI, 6.2 to 21.8) at the proximal level and by an average of 22.6% (95% CI, 8.0 to 37.2) at the middle level in comparison with the area in the control arteries (Fig. 2, *A* and *B,* and Table II). A similar significant difference was also found with the luminal radius (Table II). However, there was no significant difference at the distal level of the ITA (distal to the AVF). There was also no significant difference between the HF group and control ITAs at any level for the cross-sectional area of the media and the thicknesses of the intima, the media, and the whole wall (Table II).

For the LF group ITAs, the luminal area was significantly decreased by an average of 11.4% (95% CI, 6.4 to 16.4) at the proximal, 16.9% (95% CI, 10.9 to 22.9) at the middle, and 22.6% (95% CI, 13.8 to 31.4) at the distal portion, in comparison with the areas in the control arteries (Fig. 2, *C* and *D,* and Table II). The luminal radius was also significantly smaller at all levels. At the middle level, the cross-sectional area of the media, the thicknesses of the media, and the thicknesses of the whole wall of the

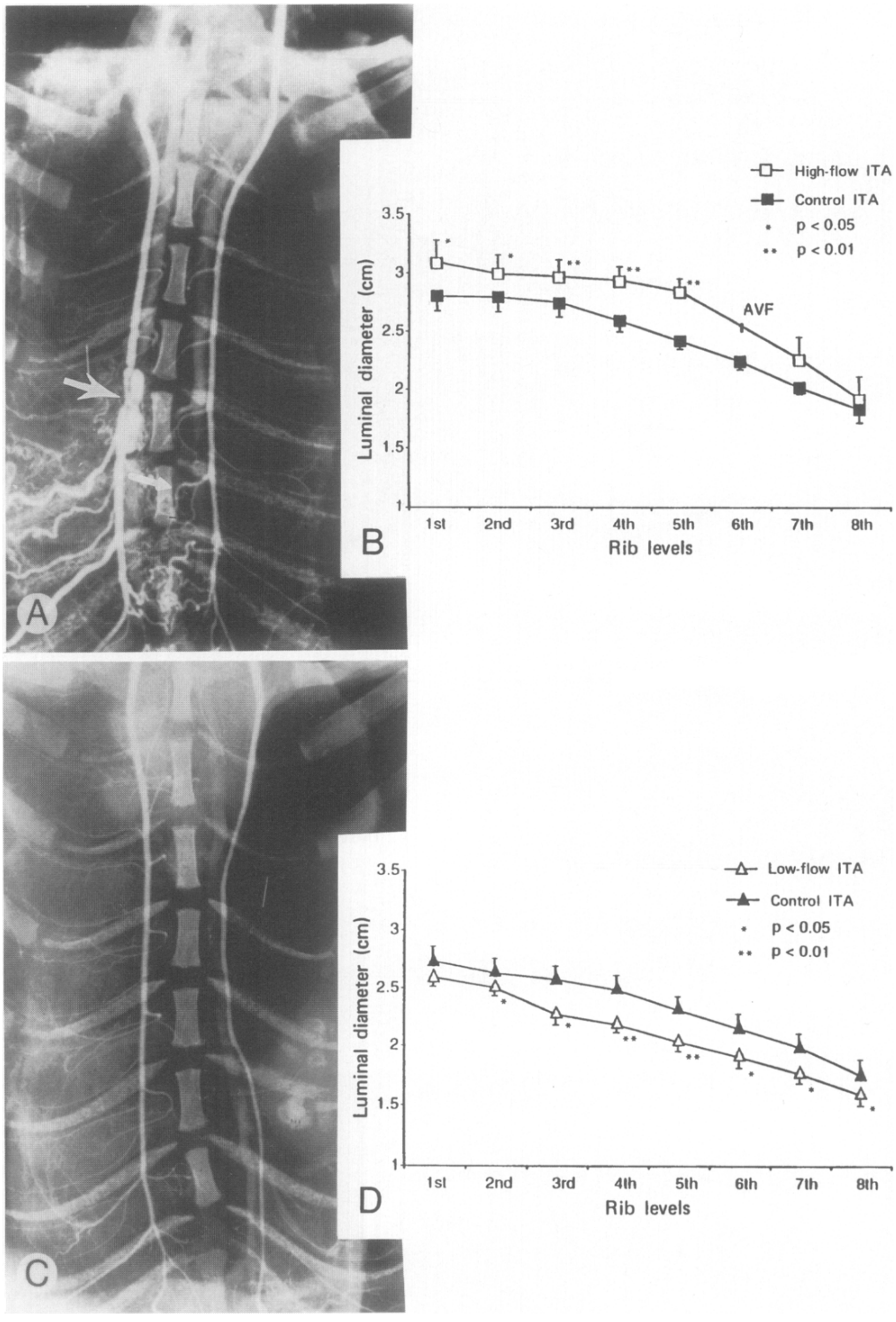

Fig. 1. Angiograms comparing representative high- and low-flow ITAs with their control arteries and diagrams of average luminal diameters showing significant differences according to rib levels between vessels with altered flow and control arteries. **A,** High-flow ITA is on *left,* with control artery on *right.* Distal ITA beyond AVF is overshadowed by accompanying internal thoracic vein, which was filled with dye from collateral circulation. **B,** Difference between average luminal diameters of high-flow ITA and control artery is significant from first to fifth rib levels (distal to AVF, what appears to be artery is vein.) **C,** Low-flow ITA is on *right,* with control artery on *left.* **D,** Difference between average luminal diameters of low-flow ITA and control artery is significant from second to eighth rib levels.

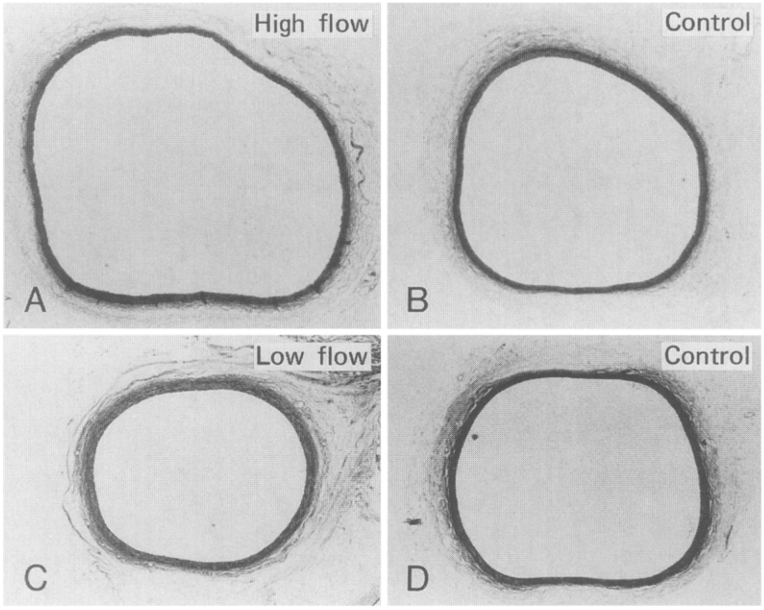

Fig. 2. Comparison of representative cross-sectional areas at middle of ITA. **A,** High-flow ITA; **B,** paired control at same level; **C,** low-flow ITA; **D,** paired control at same level. There is no evidence of intimal thickening in either case. (Hematoxylin-eosin stain; original magnification ×24.)

Table II. *Morphologic dimensional measurements from histologic sections taken from the middle of the ITAs*

	Control	*Study ITA*	*p Value*
HF group			
Luminal area (mm^2)	3.01 ± 0.73	3.61 ± 0.57	0.019*
Luminal radius (mm)	0.95 ± 0.06	1.05 ± 0.05	0.021*
Intimal thickness (mm)	0.007 ± 0.001	0.008 ± 0.001	0.473†
Medial area (mm^2)	0.49 ± 0.10	0.57 ± 0.09	0.062†
Medial thickness (mm)	0.079 ± 0.015	0.082 ± 0.012	0.535†
Wall thickness (mm)	0.118 ± 0.018	0.123 ± 0.019	0.601†
LF group			
Luminal area (mm^2)	2.64 ± 0.47	2.21 ± 0.53	0.009*
Luminal radius (mm)	0.91 ± 0.09	0.83 ± 0.11	0.002*
Intimal thickness (mm)	0.007 ± 0.002	0.008 ± 0.002	0.911†
Medial area (mm^2)	0.47 ± 0.09	0.61 ± 0.10	0.007*
Medial thickness (mm)	0.078 ± 0.009	0.108 ± 0.011	0.001*
Wall thickness (mm)	0.123 ± 0.010	0.148 ± 0.020	0.003*

Values given as mean plus or minus the standard deviation.
*Indicates significant difference.
†Indicates no significant difference.

LF group ITAs were significantly greater than those of the control arteries (Table II). There was no significant difference in intimal thickness (Table II).

Shear stress. Eight weeks after creation of the distal AVF, the calculated mean shear stress in the high-flow ITAs averaged 58.8 dynes/cm^2 (SD 16.2), which was significantly different from the average shear stress of 19.6 dynes/cm^2 (SD 6.3) for the control arteries (p = 0.035) (Table I). The shear stress in the skeletonized, dissected ITAs averaged 3.7 dynes/cm^2 (SD 0.4), which was also significantly different from the average shear stress of 10.3 dynes/cm^2 (SD 0.7) for the control arteries (p < 0.0001) (Table I).

Discussion

Clowes and Kohler[14] have pointed out that both developing and mature vessels respond to changes in blood flow by adjusting their diameters in a manner that maintains constant shear stress, and there is considerable evidence of this.[15-20] Kamiya and Togawa[15] demonstrated that increased wall shear stress induced adaptive enlargement of the arterial radius in a model with AVF in the canine carotid artery, which acted as a negative feedback to reduce shear stress. Guyton and Hartley[16] and Langille and O'Donnell[17] demonstrated that reduction in arterial diameter could be induced by decreased blood flow in the carotid arteries of rats and rabbits. Similar observations obtained from this study of canine ITAs support their findings.

Zarins and associates[18] have demonstrated with 6-month experiments in the iliac artery of cynomolgus monkeys that shear stress is normalized, or optimal shear stress is achieved, by enlargement of the artery in the case of increased flow and have suggested that intimal thickening achieves the same result in the event of reduced flow. However, in this study in the dog with 8-week flow alteration, although there was a tendency to shear stress normalization in both the HF and LF group ITAs, it did not reach the level in the control ITAs. There was also no substantial wall structural change, including no intimal thickening, in either the HF or the LF group, except for an increase in media thickness and cross-sectional area in the middle of the LF group ITAs (Table II). The differences between the study of Zarins and associates[18] and this study may be associated with the implant times and the nature of the vessels studied. The 6-month study of Zarins and associates[18] was much longer than ours, and the shear stress in our ITAs with altered flow might eventually have come close to, or reached, the normal control level with a further luminal diameter change if the study period had been longer than 8 weeks. Although medium-sized and small arteries have been classified as muscular, van Son and coworkers[21] have proposed that most of the ITA is an elastic artery with elastomuscular proximal and distal sections; this type of artery may have a different nature than the iliac artery in the monkey.

Langille, Bendeck, and Keeley[22] and Masuda and associates[19] pointed out that arterial wall remodeling was endothelium dependent and reflected a direct sensitivity of endothelial cells to the frictional force exerted on them by blood flow. Frangos and colleagues[23] hypothesized that endothelial cells are somehow capable of sensing changes in shear stress and can translate this biomechanical information into biochemical signals that then regulate the contractile state of the underlying smooth muscle cells. Therefore there may be thresholds of flow shear stress to which specific vessels respond. In this regard, the ITA may have a lesser sensitivity or broader nonresponsive tolerance than other vessels, such as carotid and iliac arteries used in similar studies. This is also supported by studies that reported no intimal thickening of the ITAs.[21, 24] This presumed broader tolerance of the ITA wall to changes in shear stress may partially explain why the ITAs maintain better patency than other autogenous grafts when used for coronary bypass.[1, 21, 25, 26] In our study, the ITA wall did seem to be relatively more sensitive to low flow than high, with an increase in the thickness of the media in the middle portion of the LF group ITAs, but not in the HF group ITAs.

Some studies have suggested that the ITA graft diameter, when used as a coronary artery bypass, is determined by the volume of blood going through it.[10, 12] Björk and associates[11] reported that preoperative overestimation of coronary artery stenosis and postoperative regression of coronary artery lesions were major factors in the reduction of ITA graft diameter. In that situation, the inflow from the proximal coronary artery is high, and the flow through the ITA graft will be low. This competitive rheologic combination may lead to narrowing of the ITA with development of the angiographic "string sign" finding.[6-8] Singh and Sosa[27] reported that an undivided major ITA side branch could cause blood steal phenomenon and result in reduction of the distal ITA lumen. Stenoses at the anastomotic site have also been reported as possible causes of postoperative narrowing of ITA grafts.[11] Our experimental results support the clinical observations that factors that diminish the ITA flow will decrease the ITA diameter. Conversely, flow through an ITA graft leads to enlargement of its caliber. The large size of the in situ ITAs in coarctation of the aorta[28, 29] is a manifestation of the same phenomenon. Again, our experimental finding is in keeping with this clinical observation (Figs. 1 and 2 and Table II).

In summary, this study demonstrated that the luminal diameter of the ITA adaptively enlarged after blood flow increase and diminished after blood flow decrease, with a tendency to normalize wall shear stress. No substantive wall structural change, including intimal thickening, was associated with either increased or decreased luminal blood flow in our 2-month observation period.

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